

4-11-00

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CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this New Application Transmittal and the documents referred to as enclosed therein are being deposited with the United States Postal Service on this date April 10, 2000 in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EL 261867320US addressed to the: Director of the United States Patent and Trademark Office., Washington, D.C. 20231.

Pamela Johnston

(Print Name)

Pamela Johnston

(Signature)

1c564 U.S. PTO

09/546143

04/10/00

Director of the United States Patent and Trademark Office
BOX PATENT APPLICATION
Washington, D.C. 20231

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110
Case Docket 9473
April 10, 2000

Sir:

Transmitted herewith for filing under 37 C.F.R. § 1.53(b) is the patent application of

Inventor(s): Peter Karl Matzinger, Michelangelo Scalone, Ulrich Zutter.

For: ASSYMETRIC SYNTHESIS PROCESS

Enclosed are:

1. _____ sheet(s) of drawing. [] formal [] informal
2. X 3 page(s) of Declaration and Power of Attorney
3. _____ page(s) of Sequence Listing
4. _____ computer disk(s) containing Sequence Listing
5. _____ Statement under 37 CFR § 1.821 or 37 C.F.R. § 1.825
6. X 24 pgs. of specification, 11 pgs. of claims, 1 pg. of abstract, Preliminary Amendment

DEPOSIT ACCOUNT

NO. 08-2525

OUR ORDER NO. 3104..

7. The fee has been calculated as shown below:

CLAIMS				
FOR	NO. FILED	NO. EXTRA	RATE	FEE
TOTAL CLAIMS	18 - 20	0	x \$18	0
INDEP. CLAIMS	10 - 3	7	x \$78	546.00
MULTIPLE DEPENDENT CLAIMS PRESENTED			+ \$260	
BASIC FEE				\$690.00
TOTAL				<u>\$ 1236.00</u>

8. X Please charge my Deposit Account No. 08-2525 in the amount of \$ 1236.00. This sheet is provided in triplicate.

9. A check in the amount of \$ to cover the filing fee is enclosed.

10. X The Commissioner is hereby authorized to charge payment of the following fees or any additional fees associated with this communication or credit any overpayment to Deposit Account No. 08-2525. This sheet is provided in triplicate.

 X Any filing fees required under 37 C.F.R. § 1.16.

 X Any patent application processing fees under 37 C.F.R. § 1.17.

11. Priority - 35 U.S.C. § 119

FOREIGN PRIORITY

[X] Foreign Priority of application(s) number 96105998.7 filed on April 17, 1996 in Europe is claimed under 35 U.S.C. § 119(a)-(d) or 35 U.S.C. § 365(a)-(b).

[X] The certified copy(ies) has(have) been filed in prior U.S. patent application Serial No. 08/832,253 on November 3, 1997.

[] The certified copy(ies) will follow.

12. RELATION BACK UNDER 35 U.S.C. § 120

(A) ☒ Amend the specification by inserting, before the first line, the following sentence: -- This is a ☐ continuation ☒ divisional of copending application(s) ☐ Serial No. 09/195,512 filed on November 19, 1998, which is a continuation of Serial No. 08/832,253 filed April 3, 1997. --

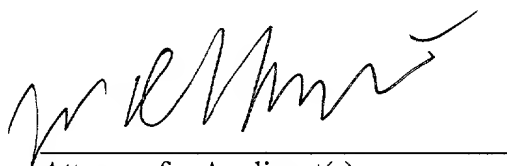
(B) ☒ A copy of the oath or declaration from the prior application noted above is enclosed.

13. ☒ The power of attorney in prior application is to:

George W. Johnston (Reg. No. 28090), William H. Epstein (Reg. No. 20008), Dennis P. Tramaloni (Reg. No. 28542) and Patricia S. Rocha-Tramaloni (Reg. No. 31054), Ellen C. Coletti (Reg. No. 34140), Raina Semionow (Reg. No. 39022), Catherine Roseman Smith (Reg. No. 34240).

- a. ☐ The power appears in the original papers of the prior application.
- b. ☐ Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.
- c. ☒ Recognize as associate attorney Lewis J. Kreisler (Reg. No. 38522).
- d. Continue to address all communications to

George W. Johnston
Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110



Attorney for Applicant(s)
William H. Epstein
(Reg. No. 20008)
Telephone: (973) 235-3723
Telefax: (973) 235-2363

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CERTIFICATION UNDER 37 CFR 1.10

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Pamela Johnston

(Print Name)

Pamela Johnston

(Signature)

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application

Peter Karl Matzinger et al.

Group:

Case Docket: 9473

Examiner:

For: ASSYMETRIC SYNTHESIS PROCESS

PRELIMINARY AMENDMENT

Nutley, New Jersey 07110

April 10, 2000

Director of the United States Patent and Trademark Office

Box Patent Application

Washington, D.C. 20231

Dear Sir:

Before examination and calculation of the fee please amend the above-identified application as follows:

In the title:

Please delete the title "ASSYMETRIC SYNTHESIS PROCESS" and replace with -- ASYMMETRIC SYNTHESIS PROCESS --.

000740" EST-9450

In the claims

On the line preceding the claims, insert -- What is claimed is: --

Please cancel claims 1-9 without prejudice.

Claim 10, line 1, change "The compounds" to -- A compound --.

Claim 12, line 1, before "compound" change "The" to -- A --.

Claim 14, line 1, before "compound" change "The" to -- A --.

Claim 15, line 1, before "compound" change "The" to -- A --.

Claim 17, line 1, before "compound" change "The" to -- A --.

Claim 19, line 1, before "compound" change "The" to -- A --.

Claim 21, line 1, before "compound" change "The" to -- A --.

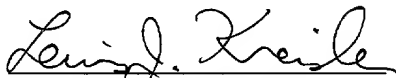
Claim 23, line 1, before "compound" change "The" to -- A --.

Claim 25, line 1, before "compound" change "The" to -- A --.

REMARKS

By this Amendment all claims, other than claims 10-27, have been canceled. Therefore claims 10-27 are pending. The independent claims have been amended to begin with the indefinite article. Entry of this Amendment is respectfully requested.

Respectfully submitted,



Attorney of Applicant(s)

Lewis J. Kreisler

(Reg. No. 38522)

340 Kingsland Street

Nutley, New Jersey 07110

Telephone: (973) 235-4387

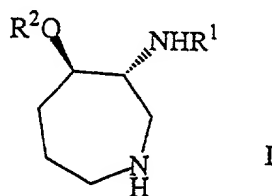
Telefax: (973) 235-2363

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The present invention is concerned with a novel process for the manufacture of azepines and with intermediates used in this process.

The present invention is concerned with a process for the
15 manufacture of azepines of the formula



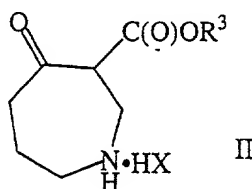
The compounds of formula I include known, pharmacologically active compounds, for example, balanol (see Int. Patent Application WO 93/03730) and other phosphokinase inhibitors, for example, the compounds described in European Patent Application A-0 663 393. The process in accordance with the invention enables such compounds to be manufactured in a simpler and more economical manner than has been possible with previously known processes.

30 In the scope of the present invention, acyl residues R¹ and R² are selected from the group consisting of benzoic acid; benzoic acid

substituted by the group selected from hydroxy, halogen, preferably fluorine, lower-alkyl and lower-alkoxy; benzoyl; and benzoyl substituted by the group selected from fluorine, lower-alkyl and lower-alkoxy. The term "lower" denotes groups with 1-6 C atoms.

- 5 Compounds of formula I in which R^2 is p-hydroxybenzoyl or p-(2-fluoro-6-hydroxy-3-methoxybenzoyl)benzoyl and R^1 is p-hydroxybenzoyl or 4-hydroxy-3,5-dimethylbenzoyl are preferred. R^4 is an amino protecting group, preferably tert.-butoxycarbonyl.

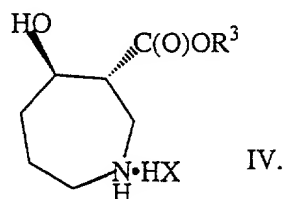
- 10 In one embodiment of the present invention, the novel process for the manufacture of compounds of formula I comprises the catalytic asymmetric hydrogenation of a compound of the formula



15

wherein R^3 is lower-alkyl and HX is an acid,

to a compound of the formula



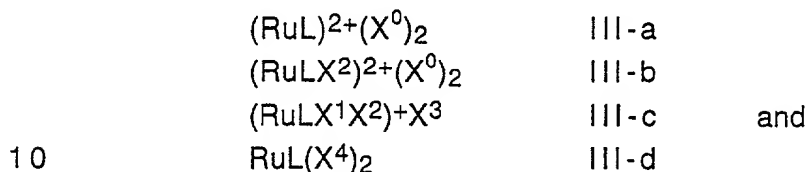
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- Examples of acids HX for the acid addition salts of formula II and formula IV are inorganic acids, such as mineral acids, for example HCl, and organic acids, such as sulphonic acids, for example, p-
 25 toluenesulphonic acid and methanesulphonic acid.

The catalyst for the asymmetric hydrogenation is a complex of an optically active, preferably atropisomeric, diphosphine ligand with a metal of Group VIII of the periodic system, especially

ruthenium. Such catalysts are described, for example, in European Patent Publication A-0 643 052.

As catalysts there come into consideration rhodium-
5 diphosphine complexes of the formulae



wherein

- | | | |
|----|-------|---|
| | X^0 | is selected from the group consisting of BF_4^- , ClO_4^- , $B(phenyl)_4^-$, SbF_6^- , PF_6^- , and $Z^1-SO_3^-$; |
| | X^1 | is halide; |
| 15 | X^2 | is benzene, hexamethylbenzene or p-cymene; |
| | X^3 | is selected from the group consisting of halide, ClO_4^- , $B(phenyl)_4^-$, SbF_6^- , PF_6^- , $Z^1-SO_3^-$ and BF_4^- ; |
| | X^4 | is selected from the group consisting of Z^2-COO^- , $Z^3-SO_3^-$, allyl and $CH_3COCH=C(CH_3)O^-$; |
| 20 | Z^1 | is halogenated lower alkyl or halogenated phenyl; |
| | Z^2 | is selected from the group consisting of lower alkyl, phenyl, halogenated lower alkyl and halogenated phenyl; |
| | Z^3 | is lower alkyl or phenyl; and |
| 25 | L | is an optically active, preferably atropiso-meric, diphosphine ligand. |

Especially preferred ligands L are

- | | | |
|----|-----------|--|
| 30 | MeOBIPHEP | (6,6'-Dimethoxybiphenyl-2,2'-diyl)bis-(diphenylphosphine); |
| | BIPHEMP | (6,6'-Dimethylbiphenyl-2,2'-diyl)bis-(diphenylphosphine); |
| 35 | BINAP | ((1,1'-Binaphthyl)-2,2'-diyl)bis-(diphenylphosphine); |

These ligands are described in Patent Publications
30 EP 643 052, EP 647 648, EP 582 692, EP 580 336, EP 690 065,
EP 643 065, JP 523 9076.

These ligands are described in Patent Publications

Diacetoxy-ruthenium-[(R)-6,6'-dimethoxybiphenyl-2,2'-diyl]bis(diphenylphosphine) [Ru(OAc)₂(R)-MeOBIPHEP] is an especially preferred catalyst.

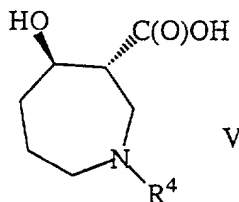
5 The ratio of ruthenium to ligand L in the complexes of formulae III-a to III-d is from about 0.5 mol to about 2 mol, preferably at about 1 mol of ruthenium per mol of ligand. The substrate/catalyst ratio (S/C; mol/mol) is from about 20 to about 30000, preferably from about 100 to about 5000.

10

The hydrogenation is carried out with the exclusion of oxygen in ethanol under an elevated pressure, for example, at pressures of from about 1 bar to about 100 bar, preferably from about 5 bar to about 70 bar, and at temperatures of from about 0°C to about 80°C, preferably from about 20°C to about 50°C.

15

The compound of formula IV is converted into a carboxylic acid compound of the formula



20

wherein R⁴ is a protecting group,

preferably a tert.-butoxycarbonyl group. The ester group R³ of the compound of formula IV is saponified using aqueous alkali, for example, sodium hydroxide solution, at room temperature. The carboxylic acid of formula V is then converted by known methods into an acid azide or acid amide containing compound of the formula

25



wherein A is azido or amino.

- 5 Subsequent degradation according to Curtius or Hofmann, yields an oxazolidone compound of the formula.



- 10 The oxazolidone of formula VI is hydrolyzed to a compound having the formula



- 15 in a manner known per se, for example, using aqueous-alcoholic alkali while heating to 70-90°C.

The hydroxy group and the amino group in the compound of formula VII are then acylated in a manner known per se, for example, by reaction with a reactive derivative of a carboxylic acid R^1COOH or R^2COOH , such as a mixed anhydride. When these carboxylic acids contain acylatable groups, such as OH groups, these groups are conveniently intermediately protected. Compounds of formula I in

which R^1 and R^2 are different from one another can be obtained, for example, by N-acylating the amino group in the compound of formula VII selectively with 1 equivalent of $R^1\text{COOH}$ and subsequently O-acylating with 1 equivalent of $R^2\text{COOH}$.

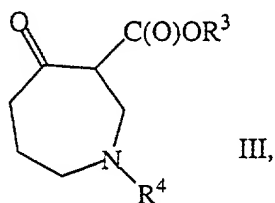
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The protecting group R^4 can be removed in a manner known per se from the compound of formula VII. For example, when R^4 is tert.-butoxycarbonyl group, R^4 can be removed by treatment with an acid, such as 2N HCl in a solvent such as ethyl acetate.

10

Another embodiment of the novel process for the manufacture of compounds of formula I, in accordance with the present invention, comprises

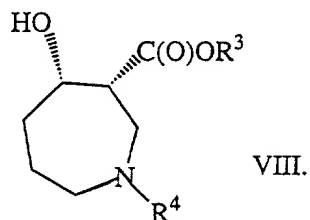
15 microbially reducing a compound of the formula



wherein R^3 is lower alkyl and R^4 is a protecting group,

20

to a compound having the formula



25 In principal, the reduction is not limited to a specific microorganism. Fungus strains (fungi), especially yeasts, are conveniently used as the microorganisms. An especially preferred microorganism is *Hanseniaspora uvarum* R 1052, especially the

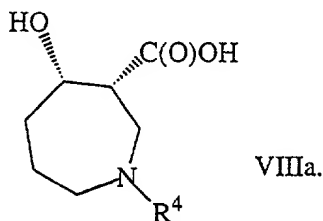
strain deposited on 16.1.1996 at the Deutschen Sammlung von Mikroorganismen und Zellkulturen (DSMZ) under No. DSM 10 496.

5 The reduction of a compound III to a compound of formula IV
can be carried out using intact cell cultures or using enzymes
obtained from the microorganisms. The preferred microorganism,
Hanseniaspora uvarum R 1052, can be cultivated in aerobic aqueous
submersed cultures on usual nutrient substrates which contain
carbon and nitrogen sources, for example, glucose or starch, and,
10 respectively, soya meal, yeast extract or peptone, as well as
inorganic salts, such as ammonium sulphate, sodium chloride or
sodium nitrate. The cultivation can be carried out at temperatures
of about 20-35°C, preferably at 27°C, in a pH range of about 3-9,
preferably at about pH 5-7.

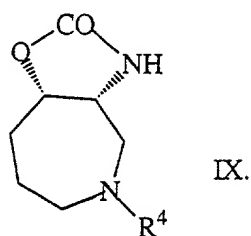
15 The compound of formula III is added to the culture of the
microorganism in an organic solvent, for example, ethyl acetate.
The course of the reduction can be followed by thin-layer chroma-
tography of samples of the reaction medium. In general, the reaction
20 takes about 8-12 hours. The reaction product, the compound of
formula VIII, can be separated from the culture solution by
extraction with a suitable organic solvent, for example, with ethyl
acetate.

25 In the next reaction step, the compound of formula VIII is
saponified, using aqueous alkali, for example, sodium hydroxide
solution, at room temperature, to its corresponding carboxylic acid.
The carboxylic acid is then converted using known methods into an
acid azide or acid amide containing compound of the formula

30

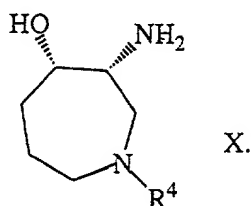


Subsequent degradation according to Curtius or Hofmann yields an oxazolidone compound of the formula



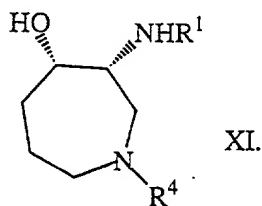
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By alkaline hydrolysis of the oxazolidone IX, for example by using aqueous-alcoholic alkali while heating to 70-90 °C, there is obtained a compound of the formula



10

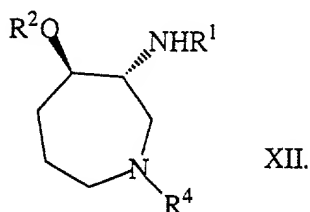
The hydroxy group and the amino group in the compound of formula X are then acylated in a manner known per se, for example, by reaction with a reactive derivative of a carboxylic acid R^1 COOH or R^2 COOH, such as a mixed anhydride. The compound of formula X is preferably N-acylated with an aromatic carboxylic acid of the formula R^1 COOH to a compound having the formula



20

The compound of formula XI is then acylated with an aromatic carboxylic acid or a reactive derivative thereof, of the formula

R²OH, in the presence of triphenylphosphine and diethyl azo-dicarboxylate, to yield a compound having the formula



5

The protecting group R⁴ can be removed in a manner known per se from the compound of formula XII. For example, when R⁴ is tert.-butoxycarbonyl group, R⁴ can be removed by treatment with an acid, such as 2N HCl in a solvent such as ethyl acetate.

The intermediate compounds of the formulae II, IV, V, VI, VIII, VIIIa, IX, X and XI as well as the compound prepared in Example 12a and, respectively, 17 are novel and are likewise objects of the present invention.

The invention is illustrated in more detail by the following Examples, however is in no manner limited thereby. In these Examples, the abbreviations used have the following significance: „ee” is „enantiomeric excess”, which is defined as percent of R-product minus percent of S-product; „dec.” is „decomposition”; HPLC is high performance liquid chromatography.

Example 1

25

Preparation of compounds of formula II and formula III.

a) A solution of 218.3 g of di-tert-butyl dicarbonate in 250 ml of dichloromethane was added at 20-25°C while stirring, in the course of 1 hour, to 101.2 g of piperidin-3-ol in 750 ml of dichloromethane. The reaction mixture was stirred at room temperature for a further 2 hours. Thereafter, a solution of 33.6 g

- of sodium bicarbonate and 11.9 g of potassium bromide in 1000 ml of deionized water was added and the reaction mixture was cooled to -2°C . After the addition of 0.39 g of 2,2,6,6-tetramethyl-piperidine 1-oxide, 560 g of 13.3% aqueous sodium hypochlorite solution were added at $0-5^{\circ}\text{C}$ in the course of 80 minutes. After stirring at -2°C for a further 30 minutes, the excess sodium hypochlorite solution was added at $0-5^{\circ}\text{C}$ in the course of 80 minutes. After stirring at -2°C for a further 30 minutes, the excess sodium hypochlorite was destroyed by the addition of about 10 ml of 38% aqueous sodium bisulphite solution. The reaction mixture was then warmed to 20°C and the aqueous layer was separated and extracted with 500 ml of dichloromethane. Both organic phases were washed with 500 ml of 10% sodium chloride solution, combined and dried over sodium sulphate. After filtration and removal of the solvent under reduced pressure the oily residue was purified by distillation under reduced pressure which yielded 191.2 g of tert-butyl 3-oxo-piperidine-1-carboxylate as a colourless oil, boiling point $80-82^{\circ}\text{C}/0.01\text{ mbar}$.
- b) 99.6 g of the compound obtained in paragraph a) were dissolved in 600 ml of diethyl ether. The solution was cooled to -70°C and the white suspension was treated simultaneously and dropwise in the course of 1 hour with solutions of 62.0 ml of ethyl diazoacetate in 125 ml of diethyl ether and 69.0 ml of boron trifluoride etherate in 125 ml of diethyl ether, with the internal temperature being held at -70°C . After stirring at -70°C for a further 1 hour the cooling bath was removed, the reaction mixture was warmed to 0°C and treated with 375 ml of 10% sodium carbonate solution. The aqueous phase was separated and extracted with 250 ml of diethyl ether. The organic phases were washed with 250 ml of 10% sodium chloride solution, combined and dried over sodium sulphate. The solvent was removed under reduced pressure at 30°C yielding ethyl 1-(tert-butoxycarbonyl)-4-oxo-azepan-3-carboxylate as a crude product in the form of a yellow oil, which was used in the next step without further purification.

- c) 147.2 g of the product obtained in paragraph b) were dissolved in 1250 ml of dioxan and seeded with 0.1 g of ethyl 4-oxo-azepan-3-carboxylate hydrobromide. Thereafter, 175 ml of 5.7M HBr/ethyl acetate were added at room temperature, while stirring, in the
- 5 course of 25 minutes. After further seeding with 0.1 g of ethyl 4-oxo-azepan-3-carboxylate hydrobromide, the suspension was stirred at room temperature for 5 hours. The crystals were filtered off, washed with ethyl acetate and dried at 50°C and 25 mbar. The resulting 91.0 g of crude ethyl 4-oxo-azepan-3-carboxylate
- 10 hydrobromide was dissolved in 1250 ml of 2-butanone while stirring and heating under reflux. The solution was cooled to 65°C and seeded with 0.1 g of pure ethyl 4-oxo-azepan-3-carboxylate hydrochloride. After cooling to room temperature, the suspension was stirred at room temperature for 1 hour and at 0°C for 3 hours.
- 15 The crystals were filtered off, washed with 200 ml of 2-butanone (cooled to -10°C) and dried at 50°C and 25 mbar, yielding 68.2 g of white ethyl 4-oxo-azepan-3-carboxylate hydrobromide, melting point 127-130°C (dec.).
- 20 d) 59.4 g of the compound obtained in paragraph b) were dissolved in 1000 ml of 1M HCl in dioxan and stirred at room temperature for 24 hours. After a reaction period of 1.5 hours the solution was seeded with about 25 mg of ethyl 4-oxo-azepan-3-carboxylate hydrochloride. The white suspension was filtered,
- 25 washed with dioxan and dried at 50°C and 25 mbar, yielding 31.3 g of ethyl 4-oxo-azepan-3-carboxylate hydrochloride in the form of white crystals, which contained about 0.4 mol of dioxan per mol of hydrochloride according to the NMR spectrum. The hydrochloride was recrystallized for further purification and in order to remove the
- 30 dioxan. 31.3 g of ethyl 4-oxo-azepan-3-carboxylate hydrochloride were dissolved in 600 ml of 2-butanol at 80°C and the solution was cooled to -20°C in the course of 2 hours and stirred at -20°C for 3 hours. The white suspension was filtered, washed with 2-butanol (cooled to -20°C) and dried at 50°C and 25 mbar to yield 22.9 g of
- 35 ethyl 4-oxo-azepan-3-carboxylate hydrochloride in the form of white crystals, melting point 145-148°C (dec.).

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Example 2

75.0 g of ethyl 4-oxo-azepan-3-carboxylate hydrochloride and
5 800 ml of ethanol were introduced into an autoclave. The autoclave
was closed and the air was removed therefrom by repeated
evacuation to about 0.1 bar and pressurization with argon (7 bar)
and hydrogen (40 bar) while stirring. Thereafter, a solution of
226 mg of diacetoxy-ruthenium (R)-6,6'-dimethoxybiphenyl-2,2-
10 diyl)-bis(diphenylphosphine) in 20 ml of ethanol was fed into the
autoclave at 2 bar hydrogen pressure with the exclusion of oxygen.
Thereafter, hydrogen pressure was increased to 40 bar and the
reaction mixture was hydrogenated while stirring at 30°C for
19 hours and at 50°C for 3 hours. Thereafter, the content of the
15 autoclave was washed out with 200 ml of ethanol and the combined
solutions were evaporated at 50°C/ 100 mbar and the brown residue
was dried for 2 hours. The residue (75.9 g, consisting of about 80%
3R,4R and 20% 3S,4R isomers) was triturated with 450 ml of
tetrahydrofuran at 24°C for 19 hours and at 16°C for 1 hour. The
20 crystals were filtered off under suction, washed with
tetrahydrofuran and dried to constant weight at 50°C/20 mbar for
3.5 hours. There were obtained 56.3 g of light beige crystals,
which were again triturated with 225 ml of tetrahydrofuran as
previously described. The crystals were removed by suction
25 filtration and dried, yielding 55.1 g of ethyl (3R,4R)-4-hydroxy-
azepan-3-carboxylate hydrobromide in the form of white crystals,
which were enantiomerically pure according to HPLC.

Example 3

30

As in Example 2, 23.2 g of ethyl 4-oxo-azepan-3-carboxylate
hydrochloride in 90 ml of ethanol were hydrogenated with a solution
of 36.1 mg of the ruthenium catalyst in 10 ml of ethanol under
40 bar hydrogen pressure at 30°C for 21 hours and at 50°C for
35 3 hours. The residue, consisting of about 80% 3R,4R and 20% 3S,4R
isomers, was triturated with tetrahydrofuran and ethanol at 50°C

5 (3R,4R)-4-hydroxy-azepan-3-carboxylate hydrochloride in the form of white crystals.

As in Example 2, 0.44 g of ethyl 4-oxo-azepan-3-carboxylate hydrochloride in 9 ml of ethanol was hydrogenated with a solution of 3.2 mg of di(η^2 -acetato)(η^4 -cycloocta-1,5-diene)-ruthenium(II) and 5.8 mg (R)-MeOBIPHEP in 1 ml of diethyl ether/THF 3/1 under 40 bar hydrogen pressure at 25°C for 23.5 hours. The yellow hydrogenation solution was evaporated on a rotary evaporator at 40°/20 mbar. With a conversion of 83%, the residue consisted, according to HPLC analysis, of 65% ethyl (3R,4R)-4-hydroxy-azepan-3-carboxylate hydrochloride with an ee >99%.

The hydrogenations set forth in Table 1 were carried out in an analogous manner to Examples 2-4.

Table 1

Asymmetric hydrogenation of ethyl 4-oxo-azepan-3-carboxylate.HX¹⁾

5

Ex No	L	X	Solv.	T °C	Press. bar	Conv./ hr	trans ³⁾		cis	
							%	ee	%	ee
5a	(S)-BINAP	Cl	2)	25	40	62/23	78	>99	22	73
5b	(R)-BIPHEMP	Cl	2)	25	40	90/23	66	94	34	38
5c	(R)-pTol- BIPHEMP	Cl	2)	25	40	93/23	72	>99	28	62
5d	(R)-p-An- MeOBIPHEP	Cl	2)	25	40	87/23	80	>99	20	77
5e	(R)-mTol- BIPHEMP	Cl	2)	25	40	90/24	58	97	42	47
5f	(R)-pDMA- MeOBIPHEP	Cl	2)	25	40	79/24	72	>99	28	95
5g	(R)-pPhenyl- MeOBIPHEP	Cl	2)	25	40	54/23	82	>99	18	26
5h	(S)-3,5-Me,4- MeO-MeOBIPHEP	Cl	2)	25	40	34/23	55	>99	45	61
5i	(R)-DiMeOBIPHEP	Cl	2)	25	40	99/23	66	>99	34	86
5j	(R)-MeOBIPHEP	Br	EtOH	40	100	99/21	76	>99	24	84
5k	"	Br	EtOH	60	100	100/21	69	>99	31	85
5l	(R)-2-Furyl- MeOBIPHEP	Br	EtOH	40	100	76/29	64	98	36	95
5m	(R)-2-Furyl-2- Biphemp	Br	EtOH	40	100	94/21	68	>99	32	69
5n	(R)-TriMeOBIPHEP	Br	EtOH	30	100	100/23	76	>99	24	95
5o	(R)-Cy2- MeOBIPHEP	Cl	EtOH	80	20	100/22	38	>99	62	92
5p	(R)-MeOBIPHEP	Cl	MeOH	30	100	100/22	75	>99	25	88
5q	"	Cl	iPrOH	"	"	90/22	78	>99	22	84
5r	"	Cl	AcOH	25	40	97/23	5	>99	95	94

000740" ET 94560

- 1) Catalyst preparation analogously to Example 2 and 3.
- 2) Catalyst preparation: in situ analogously to Example 4,
solvent: ethanol-diethyl ether-tetrahydrofuran 9:0.65:0.35.
- 3) trans: compound IV or its enantiomer. Chiral diphosphine
ligands with (R)-configuration give (3R,4R)-IV.

Example 6

As in Example 3, 3.32 g of ethyl 4-oxo-azepan-3-carboxylate hydrochloride were hydrogenated in the presence of 6.3 mg of [RuCl((R)-MeOBIPHEP)(C₆H₆)]Cl under 40 bar hydrogen pressure at 30°C for 19 hours and at 50° for 3 hours. The yellow hydrogenation solution was evaporated on a rotary evaporator at 40°/20 mbar. With a conversion of 95% the residue consisted, according to HPLC analysis, of 79% ethyl (3R,4R)-4-hydroxy-azepan-3-carboxylate with an ee >99%.

Example 7

A catalyst solution was prepared in a glove box (O₂ content < 1 ppm) by dissolving 1.3 ml of a 0.03 molar ethanolic HBr solution and 16.1 mg of Ru(OAc)₂((R)-MeOBIPHEP) in 10 ml of ethanol and stirring for 0.5 hour. Then, 0.53 g of ethyl 4-oxo-azepan-3-carboxylate hydrobromide and 2 ml of the catalyst solution prepared above were placed in 4 ml of ethanol in an autoclave and hydrogenated at 20°C under 100 bar hydrogen pressure for 21 hours. The yellow hydrogenation solution was evaporated on a rotary evaporator at 40°/20 mbar. With a conversion of 76%, the residue consisted, according to HPLC analysis, of 58% ethyl (3R,4R)-4-hydroxy-azepan-3-carboxylate hydrobromide with an ee >99%.

Example 8

- 5 A catalyst solution was prepared in a glove box (O_2 content < 1 ppm) by dissolving 1.0 ml of a 0.04 molar ethanolic HBf_4 solution and 32.1 mg of $Ru(OAc)_2((R)\text{-MeOBIPHEP})$ in 10 ml of ethanol and stirring for 0.5 hour. Then, 0.53 g of ethyl 4-oxo-azepan-3-carboxylate hydrobromide and 1 ml of the catalyst solution prepared above were placed in 9 ml of ethanol in an autoclave and hydrogenated at $20^\circ C$ under 100 bar hydrogen pressure for 21 hours.
- 10 The yellow hydrogenation solution was evaporated on a rotary evaporator at $40^\circ/20$ mbar. With a conversion of 44% the residue consisted according to HPLC analysis of 37% ethyl (3R,4R)-4-hydroxy-azepan-3-carboxylate hydrobromide with an ee >99%.

Example 9

- 67.0 g of ethyl (3R,4)-4-hydroxy-azepan-3-carboxylate hydrobromide were suspended in 500 ml of tert-butyl methyl ether and treated with 30.4 g of triethylamine. Thereafter, a solution of
- 20 54.6 g of di-tert-butyl dicarbonate in 25 ml of tert-butyl methyl ether was added at room temperature in the course of 20 minutes. Thereafter, the mixture was stirred at room temperature for a further 2 hours.
- 25 500 ml of 2N NaOH were added to the white suspension and the reaction mixture was stirred vigorously at room temperature for 2 hours. The reaction mixture was then acidified with 175 ml of 6N HCl and, after phase separation, the aqueous phase was extracted twice with 100 ml of tert-butyl methyl ether. All organic phases
- 30 were washed with 150 ml of 10% sodium chloride solution, combined and dried over sodium sulphate. After removal of the solvent under reduced pressure at $40^\circ C$ the crude hydroxyacid was dissolved in 260 ml of butyl acetate at about $85^\circ C$. After seeding with pure product the suspension was cooled to $-20^\circ C$ in the course
- 35 of 2 hours and stirred at this temperature overnight. The suspension was filtered, washed with 100 ml of hexane and dried at

50°C and 25 mbar, yielding 55.9 g of (3R,4R)-4-hydroxy-azepan-1,3-dicarboxylic acid 1-tert-butyl ester, melting point 121.5-122.5°C.

5

Example 10

300 ml of ethyl acetate and 20.9 ml of triethylamine were added to 38.9 g of the compound prepared in Example 9. The solution was heated to reflux, then 32.4 ml of diphenylphosphoryl azide were added in the course of 30 minutes and the heating under reflux was continued for a further 2 hours. After cooling to room temperature the reaction mixture was treated with 300 ml of ethyl acetate and washed with 150 ml of 5% sodium hydrogen carbonate solution and twice with 150 ml of water. The aqueous phases were extracted twice with 300 ml of ethyl acetate. The combined organic phases were dried over sodium sulphate and evaporated at 45°C under reduced pressure. The crude crystalline residue was dissolved in 300 ml of butyl acetate, seeded with pure product, cooled to -20°C in the course of about 3 hours and stirred overnight. The suspension was filtered, washed with butyl acetate (pre-cooled to -20°C) and dried at 60°C and 25 mbar to yield 29.9 g of (3aR,8aR)-5-tert-butoxycarbonyl-2-oxo-octahydro-oxazolo[4,b-c]azepine, melting point 152.5-153.5°C.

25

Example 11

25.6 g of the compound prepared in Example 10 were added to 250 ml of methanol and 250 ml of 2N NaOH. The reaction mixture was heated to reflux and held at this temperature for 3 hours. After cooling, 265 ml of solvent were distilled off at 50°C and 150 mbar and the residue was extracted three times with 200 ml of ethyl acetate each time. The three organic phases were washed with 50 ml of 10% sodium chloride solution, combined and dried over sodium sulphate. After removal of the solvent the viscous oil obtained as the residue was dissolved in 100 ml of cyclohexane at 60°C, seeded with pure product, cooled to room temperature in the

course of 2 hours and stirred overnight. The suspension was filtered, washed with 40 ml of cyclohexane and dried at 50°C and 25 mbar, yielding 21.5 g of tert-butyl (3R,4R)-3-amino-4-hydroxy-azepan-1-carboxylate, melting point 99-100.5°C.

5

Example 12

a) 4.58 g of p-toluenesulphonyl chloride dissolved in 24 ml of dichloromethane were added at room temperature in the course of 10 minutes to 4.66 g of 4-tert-butoxybenzoic acid and 6.11 g of 4-dimethylaminopyridine in 30 ml of dichloromethane. After stirring at room temperature for 2 hours, 2.30 g of the compound prepared in Example 6 in 6 ml of dichloromethane were added in the course of 10 minutes. Thereafter, the mixture was stirred at room 15 temperature for 16 hours. The reaction mixture was washed twice with 20 ml of 1N NaOH each time and then with 40 ml of 1N HCl and 40 ml of water. All aqueous phases were extracted with 20 ml of dichloromethane. The combined organic phases were dried over sodium sulphate and the solvent was removed under reduced 20 pressure. The residual white foam was chromatographed over 300 g of silica gel with 6.5 l of hexane-ethyl acetate (2:1). Fractions of 250 ml were collected. Fractions 8-25 were combined and the solvent was evaporated under reduced pressure, there being obtained 5.91 g of a white foam which was dissolved in 80 ml of heptane at 25 60°C. After stirring at -20°C overnight the crystals were filtered off, washed with cold heptane and dried at 50°C and 25 mbar to yield 5.34 g of tert-butyl (3R,4R)-3-(4-tert-butoxy-benzoylamino)-4-(4-tert-butoxy-benzoyloxy)-azepan-1-carboxylate, melting point 125.5-127.5°C.

30

b) 20.0 ml of 5M HCl in ethyl acetate were added at room temperature and while stirring to 5.83 g of the compound obtained in paragraph a) dissolved in 30 ml of ethyl acetate. The reaction mixture was stirred at room temperature overnight and the white 35 precipitate was filtered off and washed three times with 5 ml of ethyl acetate each time and dried at 50°C/25 mbar for 16 hours.

The white powder obtained was dissolved in 50 ml of water and stirred at 50°C for 1 hour. The solution was then lyophilized and yielded 3.97 g of pure 3-(4-hydroxy-benzoylamino)-4-(4-hydroxy-benzoyloxy)-hexahydroazepine hydrochloride.

5

Example 13

Hanseniaspora uvarum R 1052 was cultivated for 3 days at 27°C in a Petri dish containing a solid nutrient substrate. After
10 3 days, 100 ml of liquid nutrient medium in a 500 ml shaking flask was seeded with a loop of this culture. This pre-culture was shaken at 27°C for 18 hours. The cells grew to a density of 5×10^8 cells/ml (stationary phase). The entire pre-culture was used to inoculate a reactor which contained 7500 ml of nutrient medium
15 (containing 1% yeast extract Difco: Bacto Yeast Extract # 0127-17-9, 1% Pepton Difco: Bacto Peptone # 0118-17-0 and 2% glucose in deionized water). After 18 hours, 750 ml of 50% glucose solution and immediately thereafter 29 g of the compound prepared in Example 1b dissolved in 20 ml of ethyl acetate were added in the
20 course of 25 minutes. After 12 hours the culture solution was extracted twice with 2000 ml of ethyl acetate each time. The combined organic phases were dried over sodium sulphate. The solvent was removed under reduced pressure at 30°C to yield 30.1 g of ethyl (3R,4S)-1-(tert-butoxycarbonyl)-4-hydroxy-azepan-3-
25 carboxylate as a viscous orange oil.

Example 14

a) A mixture of 28.7 g of the compound prepared in Example 13 in
30 200 ml of tert-butyl methyl ether and 200 ml of 2N NaOH was stirred vigorously at room temperature for 4 hours and then at 50°C for 20 hours. After cooling, the aqueous phase was extracted twice with 100 ml of tert-butyl methyl ether each time. The organic phases were discarded. The aqueous phase was acidified cautiously
35 with about 70 ml of 6N HCl and extracted once with 200 ml of tert-butyl methyl ether and twice with 100 ml of tert-butyl methyl

ether each time. All three organic phases were washed once with 50 ml of 10% sodium chloride solution, combined and dried over sodium sulphate. After removal of the solvent under reduced pressure (40°C/25 mbar) the brown viscous oil was dissolved in 5 60 ml of isopropyl ether at 60°C and left to crystallize at -20°C for 16 hours. The crystals were filtered off, washed with a small amount of isopropyl ether, cooled to -20°C and dried at 40°C for 5 hours and 25 mbar, yielding 12.0 g of (3R,4S)-4-hydroxy-azepan-1,3-dicarboxylic acid 1-tert-butyl ester of melting point 98.5-10 101.5°C.

b) 140 ml of ethyl acetate, 9.8 ml of triethylamine and 15.9 ml of diphenylphosphoryl azide were added to 18.1 g of the compound obtained in paragraph a). The solution was heated to reflux for 15 2 hours, cooled, diluted with 140 ml of ethyl acetate and washed with 70 ml of 5% sodium hydrogen carbonate solution and twice with 70 ml of water each time. The three aqueous phases were separated and washed three times with 140 ml of ethyl acetate. The combined organic phases were dried over sodium sulphate and 20 the solvent was removed at 45°C/25 mbar. The crude crystalline residue was dissolved in 140 ml of butyl acetate at about 80°C, seeded with pure product, cooled and stirred at -20°C for 6 hours. The suspension was filtered, washed with butyl acetate (cooled to -20°C) and dried at 60°C and 25 mbar overnight, to yield 13.3 g of 25 tert-butyl (3aR,8aS)-2-oxo-octahydro-oxazolo[4,b-c]azepine-5-carboxylate of melting point 158-159°C.

Example 15

30 200 ml of methanol and 200 ml of 2N NaOH were added to 20.5 g of the compound prepared in Example 14b). The reaction mixture was heated to reflux and left at this temperature for 4 hours. After cooling, 200 ml of methanol were distilled off at 50°C and 150 mbar and the residue was extracted three times with 35 160 ml of ethyl acetate each time. The organic phases were washed with 40 ml of 10% sodium chloride solution, combined and dried

over sodium sulphate. After removal of the solvent, the viscous oil obtained as the residue was dissolved in 80 ml of methylcyclohexane at 50°C, seeded with pure product, cooled and stirred at 0°C for 4 hours. The crystals were filtered off, washed with 20 ml of methylcyclohexane and dried at 50°C and 25 mbar overnight, yielding 17.4 g of tert-butyl (3R,4S)-3-amino-4-hydroxy-azepan-1-carboxylate, melting point 64-67°C.

Example 16

10

9.06 g of p-toluenesulphonyl chloride in 75 ml of dichloromethane were added at room temperature to 11.5 g of 4-(tert-butoxy)-benzoic acid and 13.1 g of 4-dimethylaminopyridine in 100 ml of dichloromethane. The reaction mixture was stirred for a further 2 hours. The solution was then added in the course of 1 hour to 11.5 g of the compound prepared in Example 10 dissolved in 50 ml of dichloromethane. After stirring at room temperature for 1 hour, the reaction mixture was washed with 100 ml of 1N NaOH, 100 ml of 1N HCl and 100 ml of water. All aqueous phases were extracted with 50 ml of dichloromethane. The combined organic phases were dried over sodium sulphate and the solvent was separated under reduced pressure. The foam-like residue was dissolved in 400 ml of hot heptane and left to crystallize at room temperature overnight. The crystals were washed with 25 ml of heptane and dried at 50°/25 mbar to yield 17.3 g of tert-butyl (3R,4S)-3-(4-tert-butoxy-benzoylamino)-4-hydroxy-azepan-1-carboxylate of melting point 131.5-132.5°C.

Example 17

30

262 mg of diethyl azadicarboxylate in 2 ml of tetrahydrofuran were added while stirring to 407 mg of the compound prepared in Example 16, 253 mg of 4-(tert-butoxy)-benzoic acid and 394 g of triphenylphosphine in 8 ml of tetrahydrofuran. After stirring at 50°C for 4 hours, the solvent was removed under reduced pressure and the residue was taken up in 20 ml of cyclohexane and washed

once with 20 ml of water and twice with 10 ml of 70% methanol/water each time. The aqueous-alcoholic phase was extracted twice with 10 ml of cyclohexane each time. The combined cyclohexane phases were dried over sodium sulphate and the solvent was removed under reduced pressure. The residual viscous oil was dissolved in 10 ml of hot heptane, seeded with pure end product and left to crystallize at room temperature for 18 hours and yielded 241 mg of tert-butyl (3R,4R)-3-(4-tert-butoxy-benzoylamino)-4-(4-tert-butoxy-benzoyloxy)-azepan-1-carboxylate of melting point 126-128°C. This compound can be reacted further as in Example 12b.

Example 18

12.91 g of p-toluenesulphonyl chloride dissolved in 15 ml of dichloromethane were added at room temperature in the course of 15 minutes to 1.94 g of 4-(tert-butoxy)-benzoic acid and 2.63 g of 4-dimethylaminopyridine in 20 ml of dichloromethane. The reaction mixture was stirred for 2 hours and added in the course of 1 hour to 2.30 g of tert-butyl (3R,4R)-3-amino-4-hydroxy-azepan-1-carboxylate dissolved in 10 ml of dichloromethane. After stirring for 1 hour the reaction mixture was washed with 20 ml of 1N NaOH, 20 ml of 1N HCl and 20 ml of water. All aqueous phases were washed in succession with 10 ml of dichloromethane. The combined organic phases were dried over sodium sulphate, filtered and the solvent was evaporated. The foam-like residue obtained was dissolved in 80 ml of hot heptane and crystallized at room temperature overnight. The crystals were washed with 10 ml of heptane and dried to yield 3.23 g of tert-butyl (3R,4R)-3-(4-tert-butoxy-benzoylamino)-4-hydroxy-azepan-1-carboxylate, m.p. 134-135°C.

Example 19

572 mg of p-toluenesulphonyl chloride in 3.5 ml of dichloromethane were added at room temperature in the course of

10 minutes to 679 mg of 4-benzoyl-benzoic acid and 764 mg of 4-dimethylaminopyridine in 5 ml of dichloromethane. After further stirring at room temperature for 2 hours 1016 mg of tert-butyl (3R,4R)-3-(4-tert-butoxy-benzoylamino)-4-hydroxy-azepan-1-carboxylate in 2.5 ml of dichloromethane were added in the course of 10 minutes while stirring. Thereafter, the reaction mixture was stirred at room temperature for a further 2.5 hours and washed with 6 ml of 1N NaOH, 6 ml of 1N HCl and 6 ml of water. All aqueous phases were extracted in succession with 6 ml of dichloromethane. The combined organic phases were dried over sodium sulphate and the solvent was evaporated. The crude product was chromatographed over 100 g of silica gel with 1.4 l of hexane/ethyl acetate (2:1). Fractions of 100 ml were collected. Fractions 5-9 were combined and the solvent was evaporated. There were obtained 1.48 g of a white foam, which was crystallized from 50 ml of hot heptane, to yield 1.24 g of tert-butyl (3R,4R)-3-(4-tert-butoxy-benzoylamino)-4-(4-benzoyl-benzoyloxy)-azepan-1-carboxylate, m.p. 145-148°C, as a white powder.

20

Example 20

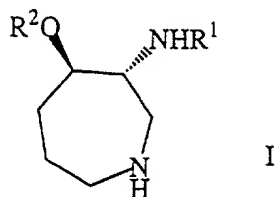
3.0 ml of 5N HCl in ethyl acetate were added at room temperature while stirring to 922 mg of the azepine prepared in Example 19 in 4.0 ml of ethyl acetate. The reaction mixture was stirred at room temperature overnight and the precipitate was filtered off, washed three times with 2 ml of ethyl acetate and dried at 50°C/25 mbar for 16 hours yielding 0.70 g of 3-(4-hydroxy-benzoylamino)-4-(4-benzoyl-benzoyloxy)-hexahydroazepine hydrochloride.

30

Claims

1. A process for the manufacture of compounds of the formula

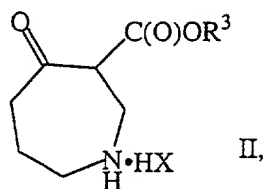
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wherein R¹ and R² are independently an acyl residue of an aromatic carboxylic acid,

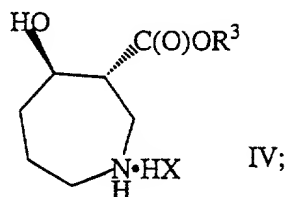
10 comprising:

- a) asymmetrically hydrogenating a compound of the formula



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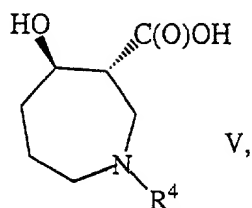
wherein R³ is lower-alkyl,
to a compound of the formula



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- b) providing a protecting group to the compound of formula IV;

c) saponifying the compound of formula IV after step b), forming a compound of the formula

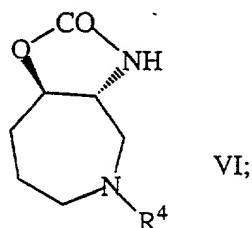


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wherein R^4 is a protecting group;

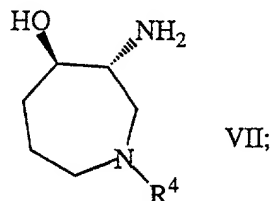
d) converting the compound of formula V into a compound of the formula

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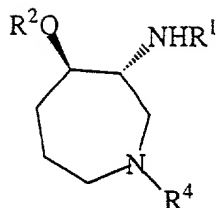
e) hydrolyzing the compound of formula VI into a compound of the formula

15



f) N- and, respectively, O-acylating the compound of formula VII with an aromatic carboxylic acid of the formula R^1COOH or R^2COOH to form a compound of the formula

20



XII; and

g) cleaving off protective groups on the compound of formula XII, to form the compound of formula I.

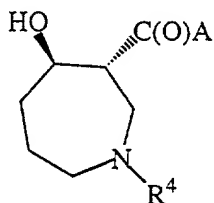
5

2. The process of claim 1, wherein R¹ and R² are p-hydroxybenzoyl.

3. The process of claim 1, further comprising in step c

10

i) converting the compound of formula V into a compound of the formula



Va,

15

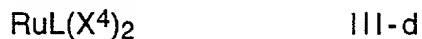
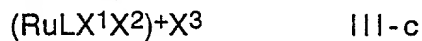
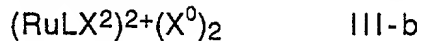
wherein A is azido or amino; and

ii) performing a Curtius or Hofmann degradation on the compound of formula Va to yield the compound of formula VI.

20

4. The process of claim 1, wherein the compound of formula II is hydrogenated in the presence of a rhodium-diphosphine complex catalyst having a formula selected from the formulae

25



and

X^0 is selected from the group consisting of BF_4^- , ClO_4^- , $B(phenyl)_4^-$, SbF_6^- , PF_6^- and $Z^1-SO_3^-$;
 X^1 is halide;
5 X^2 is benzene, hexamethylbenzene or p-cymene;
 X^3 is selected from the group consisting of halide, ClO_4^- , $B(phenyl)_4^-$, SbF_6^- , PF_6^- , $Z^1-SO_3^-$ and BF_4^- ;
 X^4 is selected from the group consisting of Z^2-COO^- , $Z^3-SO_3^-$, allyl and $CH_3COCH=C(CH_3)O^-$;
10 Z^1 is halogenated lower alkyl or halogenated phenyl;
 Z^2 is selected from the group consisting of lower alkyl, phenyl, halogenated lower alkyl and halogenated phenyl;
phenyl;
15 Z^3 is lower alkyl or phenyl; and
L is an optically active atropiso-meric, diphosphine ligand.

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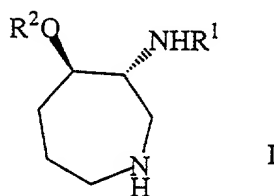
pDMA-MeOBIPHEP 6,6'-Dimethoxy-P,P',P',P'-tetrakis-(4-dimethylamino-phenyl)-biphenyl-2,2'-bis-phosphine;

pPhenyl-MeOBIPHEP	(6,6'-Dimethoxybiphenyl-2,2'-diyl)-bis(bis-(biphenyl)-phosphine);
mTol-BIPHEMP	(6,6'-Dimethylbiphenyl-2,2'-diyl)bis(di-(m-tolyl)phosphine);
5 Cy ₂ -MeOBIPHEP	P ₂ ,P ₂ -Dicyclohexyl-6,6'-dimethoxy-P ₂ ',P ₂ '-diphenyl-biphenyl-2,2'-bis-phosphine;
2-Furyl ₂ -BIPHEMP	P,P-Diphenyl-P',P'-di-2-furyl-(6,6'-dimethyl-biphenyl-2,2'-diyl)diphosphine;
10 (3,5-Me,4-MeO)-MeOBIPHEP	6,6'-Dimethoxy-P,P,P',P'-tetrakis-(dimethyl-4-methoxy-phenyl)-biphenyl-2,2'-bis-phosphine;
DiMeOBIPHEP	(5,5',6,6'-Tetramethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine);
15 TriMeOBIPHEP	(4,4',5,5',6,6'-Hexamethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine); and
2-Furyl-MeOBIPHEP	(6,6'-Dimethoxybiphenyl-2,2'-diyl)bis-(di-2-furylphosphine).

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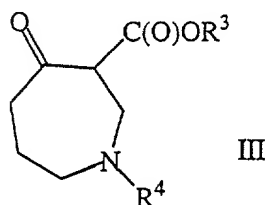
6. The process of claim 5, wherein the catalyst is Ru(OAc)₂(R)-MeOBIPHEP.

25 7. A process for the manufacture of compounds of the formula



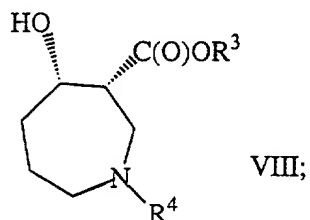
wherein R^1 and R^2 are independently an acyl residue of an aromatic carboxylic acid, comprising:

- 5 a) microbially reducing a compound of the formula

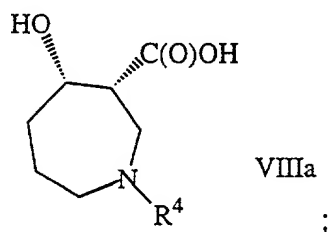


wherein R^3 is lower-alkyl and R^4 is a protecting group,

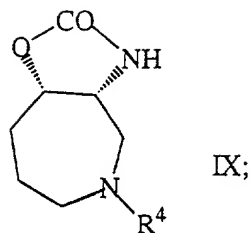
- 10 to a compound of the formula



- 15 b) saponifying the compound of formula VIII to a compound of the formula

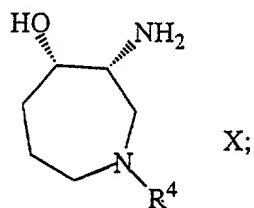


- 20 c) transforming the compound of formula VIIIa into a compound of the formula



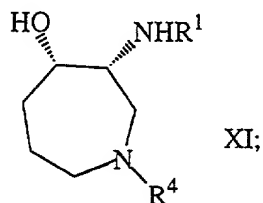
d) hydrolyzing the compound of formula IX into a compound of the formula

5



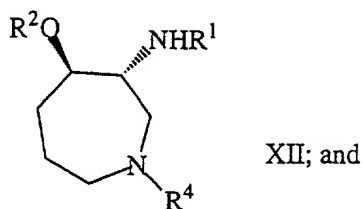
e) acylating the compound of formula X with an aromatic carboxylic acid of the formula R^1COOH to a compound of the formula

10



f) acylating the compound of formula XI with an aromatic carboxylic acid or a reactive derivative thereof, to form a compound of the formula

15



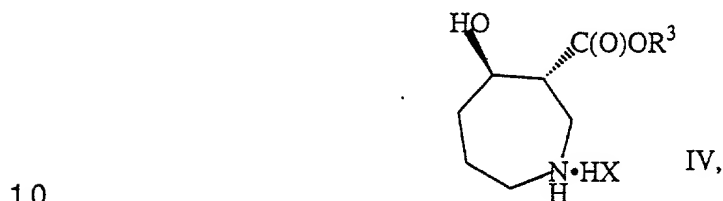
g) cleaving off the protecting group R^4 from the compound of formula XII yielding the compound of formula I.

20

8. The process of claim 7, wherein the compound of formula III is reduced using a culture of *Hanseniaspora uvarum* R 1052.

5 9. The process of claim 7, wherein R^1 and R^2 are p-hydroxybenzoyl.

10. The compounds of the formula



wherein R^3 is lower alkyl.

11. The compound of claim 10, ethyl (3R,4R)-4-hydroxy-
15 azepan-carboxylate hydrochloride.

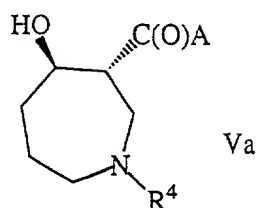
12. The compound of the formula



wherein R^4 is a protecting group.

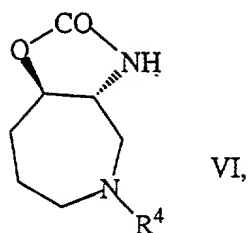
13. The compound of claim 12, (3R,4R)-4-Hydroxy-azepan-
1,3-dicarboxylic acid 1-tert.-butyl ester.
25

14. The compound of the formula



5 wherein A is azido or amino and R⁴ is a protecting group.

15. The compound of the formula



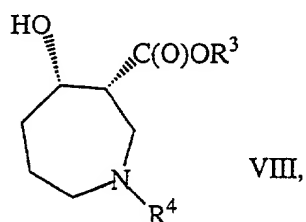
10

wherein R⁴ is a protecting group.

16. The compound of claim 15, (3aR,8aR)-5-tert-Butoxycarbonyl-2-oxo-octahydro-oxazolo(4,b-c)azepine.

15

17. The compound of the formula

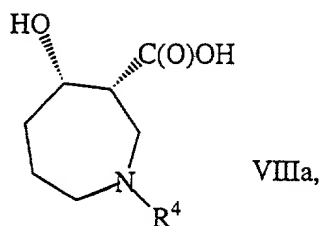


20

wherein R³ is lower alkyl and R⁴ is a protecting group.

18. The compound of claim 17, ethyl (3R,4S)-1-(tert-butoxycarbonyl)-4-hydroxy-azepan-3-carboxylate.

19. The compound of the formula



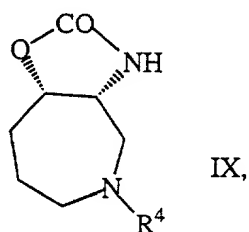
5

wherein R^4 is a protecting group.

20. The compound of claim 19, (3R,4S)-4-Hydroxy-azepan-1,3-dicarboxylic acid 1-tert-butyl ester.

10

21. The compound of the formula



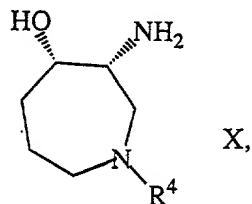
15

wherein R^4 is a protecting group.

22. The compound of claim 21, tert-Butyl (3aR,8aS)-2-oxo-octahydro-oxazolo(4,b-c)azepine-5-carboxylate.

20

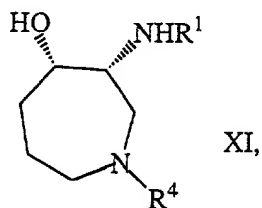
23. The compound of the formula



wherein R^4 is a protecting group.

24. The compound of claim 23, tert-Butyl (3R,4S)-3-amino-4-hydroxy-azepan-1-carboxylate.

5 25. The compound of the formula



wherein R^4 is a protecting group.

10

26. The compound of claim 25, tert-Butyl (3R,4S)-3-(4-tert-butoxy-benzoylamino)-4-hydroxy-azepan-1-carboxylate.

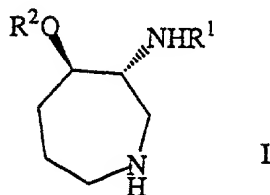
27. The compound tert-Butyl (3R,4R)-3-(4-tert-butoxy-
15 benzoylamino)-4-(4-tert-butoxy-benzoyloxy)-azepan-1-carboxylate.

* * *

Abstract

5

A novel process for the manufacture of compounds of the formula



10 wherein R¹ and R² independently represent aroyl.

The present invention also concerns novel intermediates used in the novel process for making compounds of formula I.

000000-044000

Declaration and Power of Attorney for Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

ASYMMETRIC SYNTHESIS PROCESS

the specification of which

(check one)

☒ is attached hereto

☐ was filed on _____ as

Application Serial No. _____

and was amended on _____

(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

Priority Claimed

<u>96105998.7</u>	<u>Europe</u>	<u>17 / April / 1996</u>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
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(Number)	(Country)	(Day/Month/Year Filed)	Yes	No
<u> </u>	<u> </u>	<u> </u>	<input type="checkbox"/>	<input type="checkbox"/>
(Number)	(Country)	(Day/Month/Year Filed)	Yes	No

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	2113	2114	2115	2116	2117	2118	2119	2120	2121	2122	2123	2124	2125	2126	2127	2128	2129	2130	2131	2132	2133	2134	2135	2136	2137	2138	2139	2140	2141	2142	2143	2144	2145	2146	2147	2148	2149	2150	2151	2152	2153	2154	2155	2156	2157	2158	2159	2160	2161	2162	2163	2164	2165	2166	2167	2168	2169	2170	2171	2172	2173	2174	2175	2176	2177	2178	2179	2180	2181	2182	2183	2184	2185	2186	2187	2188	2189	2190	2191	2192	2193	2194	2195	2196	2197	2198	2199	2200	2201	2202	2203	2204	2205	2206	2207	2208	2209	2210	2211	2212	2213	2214	2215	2216	2217	2218	2219	2220	2221	2222	2223	2224	2225	2226	2227	2228	2229	2230	2231	2232	2233	2234	2235	2236	2237	2238	2239	2240	2241	2242	2243	2244	2245	2246	2247	2248	2249	2250	2251	2252	2253	2254	2255	2256	2257	2258	2259	2260	2261	2262	2263	2264	2265	2266	2267	2268	2269	2270	2271	2272	2273	2274	2275	2276	2277	2278	2279	2280	2281	2282	2283	2284	2285	2286	2287	2288	2289	2290	2291	2292	2293	2294	2295	2296	2297	2298	2299	2300	2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312	2313	2314	2315	2316	2317	2318	2319	2320	2321	2322	2323	2324	2325	2326	2327	2328	2329	2330	2331	2332	2333	2334	2335	2336	2337	2338	2339	2340	2341	2342	2343	2344	2345	2346	2347	2348	2349	2350	2351	2352	2353	2354	2355	2356	2357	2358	2359	2360	2361	2362	2363	2364	2365	2366	2367	2368	2369	2370	2371	2372	2373	2374	2375	2376	2377	2378	2379	2380	2381	2382	2383	2384	2385	2386	2387	2388	2389	2390	2391	2392	2393	2394	2395	2396	2397	2398	2399	2400	2401	2402	2403	2404	2405	2406	2407	2408	2409	2410	2411	2412	2413	2414	2415	2416	2417	2418	2419	2420	2421	2422	2423	2424	2425	2426	2427	2428	2429	2430	2431	2432	2
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(Status)
(patented, pending, abandoned)

(Status)
(patented, pending, abandoned)

(Supply similar information and signature for third and subsequent joint inventors.)

Full name of sole or third inventor, if any

Ulrich Zutter

Inventors signature

Ulrich Zutter

Date

March 17, 1997

Residence

Basle, Switzerland

Citizenship

Switzerland

Post Office Address

33 Socinstrasse, CH-4051 Basle, Switzerland

Title 37, Code of Federal Regulations, §1.56, duty to disclose information material to patentability (in part) provides, in part, that each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is cancelled or withdrawn from consideration, or the application becomes abandoned.

Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and

- (1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim: or
- (2) It refutes, or is inconsistent with, a position the applicant takes in:
 - (i) Opposing an argument of unpatentability relied on by the Office, or
 - (ii) Asserting an argument of patentability.